Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 2457–2462

TETRAHEDRON

Efficient synthesis of (*R*)- and (*S*)-3-octanol, (*R*)-2-dodecanol, (*R*)-2-methyl-4-heptanol and (*R*)-2-methyl-4-octanol: the pheromones of *Myrmica scabrinodis*, *Crematogaster castanea*, *C. liengmei*, *C. auberti* and *Metamasius hemipterus*

Byung Tae Cho* and Dong Jun Kim

Department of Chemistry, Hallym University, Chunchon 200702, South Korea

Received 14 January 2003; revised 16 February 2003; accepted 17 February 2003

Abstract—A simple and efficient synthesis of optically active insect pheromones, such as (*R*)- and (*S*)-3-octanol, (*R*)-2-dodecanol, (*R*)-2-methyl-4-heptanol and (*R*)-2-methyl-4-octanol starting from non-racemic β-hydroxy sulfides has been established.

1. Introduction

Recently much interests on optically active insect pheromones are rapidly growing since their enantiomers have commonly different biological activities.[1] For example, (*R*)-3-octanol (**1**) is the sex attractant pheromone of *Myrmica scabrinodis*,[2] whereas its *S*-enantiomer is an alarm pheromone found in the ants *Crematogaster castanea* and *C. liengmei*.[3] On the other hand, (*R*)-2-dodecanol (**2**) is a component of the hind leg tibial gland secretion of worker ants of *C. auberti*.[4] (*R*)-2-Methyl-4-heptanol (**3**) and (*R*)-2-methyl-4-octanol (**4**) are identified as the male-produced aggregation pheromones of the West Indian sugarcane weevils *Metamasius hemipterus*[5] (Fig. 1). It has been reported that biological activities of these pheromones exhibit that their (*R*)-isomers are far more potent than (*S*)-isomers.[4,5] Methods for the synthesis of these chiral insect pheromones include enzymatic resolution of racemic secondary alkyl acetates for **1** and **2**,[6,7] alkylation of optically active intermediates starting from chiral substances such as methyl (*R*) or (*S*)-3-hydroxypentanoate,[8,9] and (*S*)-leucine for **3** and **4**.[10] These pheromones are simple secondary aliphatic alcohols. One of the most efficient methods for obtaining optically active secondary alcohols is the asymmetric reduction of prochiral ketones. Although a number of stoichiometric and catalytic asymmetric reducing agents have been published,[11] successful reductions for unhindered aliphatic ketones to give high enantioselectvity are quite rare.[12] Recently we discovered that optical purities

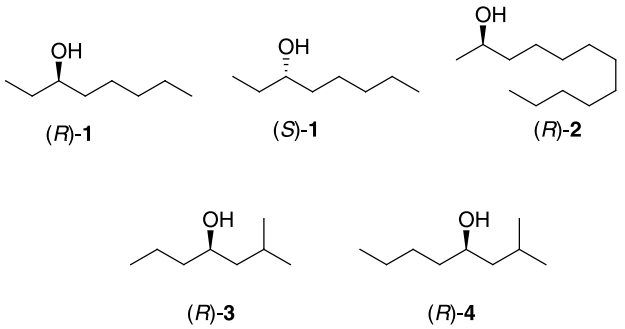


Figure 1.

of aliphatic β-hydroxy sulfides could be simply upgraded by a recrystallization of their 3,5-dinitrobenzoates. Since these β-hydroxy sulfides could be converted to optically active secondary alcohols by in turn oxidation to β-hydroxy sulfoxides, alkylation to dianions of the sulfoxides, and desulfurization of the α-alkylated sulfoxides,[13] this finding led us promptly to developing a new convenient route for the synthesis of optically active pheromones **1**–**4** using the β-hydroxy sulfides as starting materials.

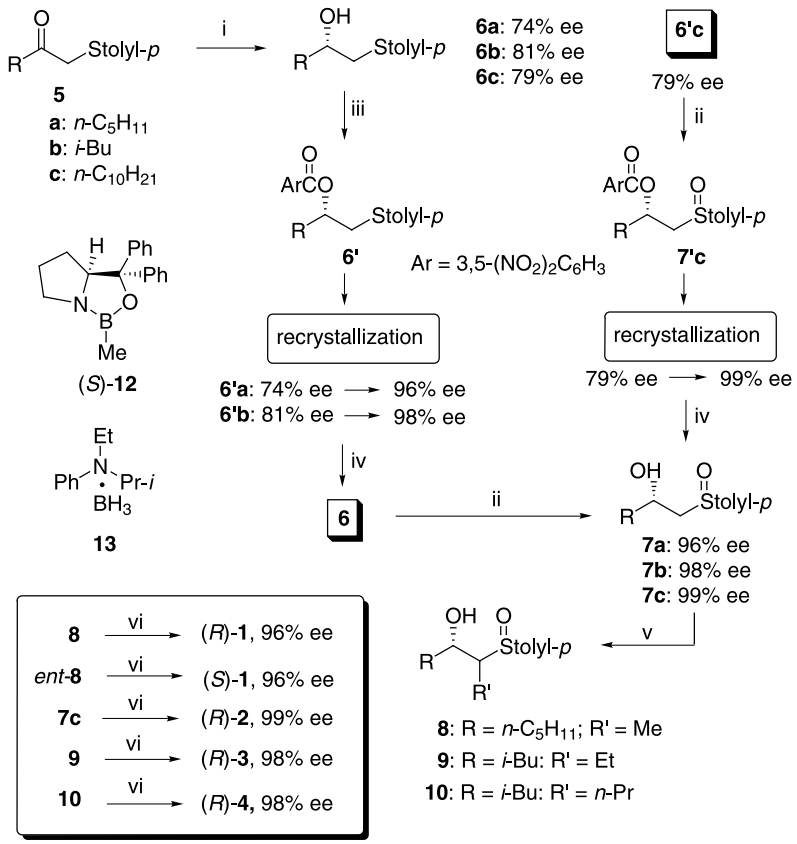
2. Results and discussion

Prior to performing this study, we first examined the synthesis of chiral pheromones (*R*)-**1** and (*R*)-**3** by asymmetric reduction of 3-octanone and 2-methyl-4-heptanone with (*S*)-MeCBS-oxazaborolidine (**12**)-catalyzed borane, which is one of the promising chiral reducing agents for prochiral ketone reduction. Unfortunately, the reduction provided corresponding alcohols with moderate to low

Keywords: chiral insect pheromone; asymmetric reduction; chiral β-hydroxy sulfides; dianion alkylation.

* Corresponding author. Tel.: +82-33-240-8491; fax: +82-33-251-8491; e-mail: btcho@hallym.ac.kr

0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00254-0



Scheme 1. (i) (*R*) or (*S*)-MeCBS oxazaborolidine (**12**, 0.1 equiv.), *N*-ethyl-*N*-isopropylaniline–borane complex (**13**, 1.0 equiv.), THF, 25°C 98–99%. (ii) *m*-CPBA (1.1 equiv.), CH_2Cl_2, room temperature, 92–95%. (iii) 3,5-$(NO_2)_2C_6H_3COCl$ (1.5 equiv.), TMEDA (1.0 equiv.), CH_2Cl_2, 97–99%. (iv) 2N NaOH, MeOH, room temperature, 98–99%. (v) *n*-BuLi (2.8 equiv.), R′I (1.1 equiv.), THF, −78–20°C, 72–93%. (vi) Raney Ni, MeOH, room temperature, 89–92%.

enantioselectivity, such as (*R*)-**1** with 61% ee and (*R*)-**3** with 18% ee. The synthetic routes for preparation of chiral pheromones **1**–**4** using chiral β-hydroxy sulfides **6** as staring materials are outlined in Scheme 1. The starting material **6** was prepared by (*R*) or (*S*)-**12**-catalyzed reduction of β-keto sulfides **5** according to our previous procedure.[14] The reduction provided **6** with 74–81% ee in nearly quantitative yields. Enantiomeric purities of **6** obtained were determined by HPLC analysis using a 25 cm Whelk-O1 or Chiralcel OD-H chiral column. Acylation of **6** with 1.5 equiv. of 3,5-dinitrobenzoyl chloride in the presence of 1.0 equiv. of TMEDA in dichloromethane[15] at room temperature provided 3,5-dinitrobenzoates **6′** of the corresponding alcohols in 96–98% yield as light yellow solids. To improve optical purities of **6′**, these were recrystallized in appropriate solvents. Thus optical purity of **6′a** was increased from 74% ee to 96% ee by twice recrystallization in ethyl ether and that of **6′b** was increased from 81% ee to 98% ee by a single recrystallization in ethyl acetate. However, the improvement for **6′c** was unsuccessful. Instead, this was successfully achieved by a single recrystallization of a diastereomeric mixture of sulfoxide ester **7′c** from dichloromethane–hexane. The sulfoxide ester **7′c** was prepared in 93% yield by oxidation of **6c** with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane at 0°C. Optical purity of **7′c** after recrystallization was increased from 79% ee to 99% ee.[16] The results are summarized in Table 1. These esters were hydrolyzed with 2N NaOH in methanol at room temperature to give **6a**,**b** and **7c** without racemization. Alkylation to the dianions of β-hydroxy sulfoxides with alkyl iodides[17] was carried out as follows. Oxidation of (*S*)-**6a** with 96% ee and (*S*)-**6b** with 98% ee with *m*-CPBA in dichloromethane at room temperature afforded β-hydroxy sulfoxides (*S*)-**7a** and (*S*)-**7b** in 92 and 95% yield, respectively.[18] After (*S*)-**7a** was treated with 2.8 equiv. of *n*-butyl lithium in THF at −78°C,

Table 1. Preparation of optically active **6**

Before recrystallization[a]			After recrystallization[a]		
Compound	Yield (%)[b]	% ee	Yield (%)[b]	% ee	Configuration
6a	98	74[c],[14]	62[d]	96[c]	*S*
ent-**6a**	98	76[c]	64[d]	96[c]	*R*
6b	97	81[c],[14]	80[f]	98[e]	*S*
6c	99	79[c]	51[g]	99[c]	*S*

Compound **6** was prepared by the reduction of β-keto sulfides **5** using 1.0 equiv. of *N*-ethyl-*N*-isopropylaniline–borane complex **13** in the presence of 0.1 equiv. of CBS-oxazaborolidine **12** in THF at 25°C; Ref. 14.

[a] Achieved by recrystallization of 3,5-dinitrobenzoates of **6** or its sulfoxide **7c**.

[b] Isolated yield.

[c] Determined by HPLC analysis using a Whelk-O1 chiral column.

[d] Isolated yield obtained from twice recrystallization of 3,5-dinitrobenzoate of **6a** or *ent*-**6a** from ethyl ether, followed by hydrolysis of the ester.

[e] Determined by HPLC analysis using a Chiralcel OD-H chiral column.

[f] Isolated yield obtained from a single recrystallization of 3,5-dinitrobenzoate of **6b** from ethyl acetate, followed by hydrolysis of the ester.

[g] Isolated yield obtained from a single recrystallization of 3,5-dinitrobenzoate of **7c** from dichloromethane–hexane, followed by hydrolysis of the ester and subsequent deoxygenation.

followed by addition of 1.1 equiv. of methyl iodide, the reaction mixture was allowed to warm to 20°C to give α-methylated sulfoxide **8** in 93% yield. Treatment of **8** with Raney-nickel[19] in methanol at room temperature provided (*R*)-3-octanol with 96% ee in 90% yield. The result indicates that no racemization occurs during sulfoxidation, alkylation and desulfurization. Using the same methodology, (*S*)-**1** with 96% ee from *ent*-**8** was obtained. Similarly, desulfurization of **7c**, of which optical purity was improved by recrystallization of **7′c** afforded (*R*)-**2** with 99% ee. The same method for **9** and **10** obtained by α-alkylation of (*S*)-**7b** with ethyl iodide and *n*-propyl iodide, respectively, provided (*R*)-**3** and (*R*)-**4** with 98% ee.

3. Conclusion

We have established a new and simple synthesis of optically active insect pheromones, such as (*R*)- and (*S*)-3-octanol, (*R*)-2-dodecanol, (*R*)-2-methyl-4-heptanol, and (*R*)-2-methyl-4-octanol starting from non-racemic β-hydroxy sulfides. This method provided a general route for preparing both *R* and *S* enantiomers of such pheromones with high enantiomeric purities.

4. Experimental

4.1. General

All operations with air-sensitive materials were carried out under a nitrogen atmosphere in oven-dried glassware. Liquid materials were transferred with a double-ended needle. The reactions were monitored by TLC using silica gel plates and the products were purified by flash column chromatography on silica gel (Merck; 230–400 mesh). NMR spectra were recorded at 200, 300 or 400 MHz for ^{1}H and 50, 75 or 100 MHz for ^{13}C using Me_4Si as the internal standard in $CDCl_3$. Optical rotations were measured with a high-resolution digital polarimeter. Melting points were uncorrected. Enantiomeric excesses (ees) of the products were determined by HPLC analyses using a 4.6×25 mm Whelk-O1 (Regis), Chiralpak OT or Chiralcel OD-H (Daicel) chiral column and GC analysis using a 0.25 mm×30 m β-DEX 120 (Supelco) or G-TA (Astec) chiral capillary column.

4.2. Materials

Most of organic compounds utilized in this study were commercial products of the highest purity. They were further purified by distillation when necessary. THF was distilled over sodium benzophenone ketyl and stored in ampules under nitrogen atmosphere. The CBS reagent **12** and *N*-ethyl-*N*-isopropylaniline–borane complex **13** were purchased from the Aldrich Chemical Company, Inc.

4.3. Preparation of optically active β-hydroxy sulfides 6

According to our previous procedure,[14] (*S*)-**6a** with 74% ee and (*S*)-**6b** with 81% ee were prepared by (*S*)-CBS oxazaborolidine (**12**)-catalyzed reduction of β-keto sulfides **5** using **13** as the hydride source. Using the same methodology, *ent*-**6a** and (*S*)-**6c** were prepared.

4.3.1. (2*R*)-(−)-1-(*p*-Toluenesulfanyl)-2-heptanol *ent*-6a. R_f 0.4 (EtOAc/hexane 1:4); oil; 98% yield; IR (neat, cm^{-1}): 3404, 2911, 1490, 799; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (t, 3H, J=6.4 Hz), 1.27–1.49 (m, 8H), 2.32 (s, 3H), 2.45 (d, 1H, J=3.1 Hz), 2.78 (dd, 1H, J=9.0, 13.6 Hz), 3.11 (dd, 1H, J=3.2, 13.6 Hz), 3.63 (m, 1H), 7.11 (d, 2H, J=7.9 Hz), 7.31 (d, 2H, J=8.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.67, 21.73, 23.22, 26.02, 32.46, 36.68, 43.68, 69.88, 130.57, 131.61, 132.05, 137.61. Calcd for $C_{14}H_{22}OS$: C, 70.54; H, 9.30; S, 13.45. Found: C, 70.46; H, 9.36; S, 13.51; $[\alpha]_D^{22}$=−35.6 (*c* 1.12, $CHCl_3$), *R*; HPLC analysis using a Whelk-O1 chiral column [*iso*-PrOH/hexane: 1:9; flow rate: 0.3 mL/min; detector: 254 nm] showed it to be 76% ee [t_R (*S*) 26.83 min and t_R (*R*) 28.72 min].

4.3.2. (2*S*)-(+)-1-(*p*-Toluenesulfanyl)-2-dodecanol 6c. R_f 0.47 (EtOAc/hexane 1:4); white solid; mp 38–40°C; 99% yield; IR (neat, cm^{-1}): 3382, 2915, 801; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (t, 3H, J=6.41 Hz), 1.25–1.58 (m, 18H), 2.32 (S, 3H), 2.45 (d, 1H, J=3.36 Hz), 2.78 (dd, 1H, J=8.85, 13.74 Hz), 3.10 (dd, 1H, J=3.36, 13.74 Hz), 3.62 (m. 1H), 7.11 (d, 2H, J=8.55 Hz), 7.31 (d, 2H, J=7.94 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.76, 21.67, 23.34, 26.34, 29.99, 30.21, 30.26, 32.57, 36.75, 43.70, 69.96, 131.61, 130.57, 132.17, 137.60. Calcd for $C_{19}H_{32}OS$: C, 73.97; H, 10.45; S, 10.39. Found: C, 73.99; H, 10.63; S, 10.29; $[\alpha]_D^{20}$=+24.96 (*c* 1.21, $CHCl_3$), *S*; HPLC analysis using a Whelk-O1 column [*iso*-PrOH/hexane: 1:99; flow rate: 0.3 mL/min; detector: 254 nm] showed it to be 79% ee [t_R (*S*) 22.85 min and t_R (*R*) 24.55 min].

4.4. General procedure for preparation of 3,5-dinitrobenzoates of 6 and improvement of their optical purities

To a mixture of **6a**, *ent*-**6a**, **6b** or **6c** (5 mmol) and TMEDA (5 mmol) in dichloromethane (20 mL) was added a solution of 3,5-dinitrobenzoyl chloride (7.5 mmol) in dichloromethane (20 mL) containing 2 drops of THF and the mixture was stirred at room temperature for 12 h. To this was added a saturated $NaHCO_3$ solution (20 mL) with vigorous stirring. Organic layer was separated and then aqueous layer was extracted with dichloromethane (3×20 mL). Combined extract was dried over anhydrous Na_2SO_4, filtered and concentrated to give **6′a**–**c** in nearly quantitative yields. The esters **6′** obtained were recrystallized with appropriate solvents.

4.4.1. Compound 6′a and *ent*-6′a. 98% Yield; light yellow solid; IR (KBr, cm^{-1}): 2980, 1728, 1545, 1344, 1273, 1167, 1076; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (t, 3H, J=6.10 Hz), 1.31–1.83 (m, 8H), 2.16 (s, 3H), 3.23 (d, 2H, J=5.49 Hz), 5.37 (m, 1H), 6.97 (d, 2H, J=7.94 Hz), 7.28 (d, 2H, J=7.94 Hz), 8.95 (d, 2H, J=2.14 Hz), 9.19 (t, 1H, J=2.14 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.61, 21.51, 23.09, 25.59, 32.10, 33.96, 39.04, 77.41, 122.83, 130.08, 130.47, 131.60, 132.36, 134.47, 137.55, 149.12, 162.70. Calcd for $C_{21}H_{24}N_2O_6S$: C, 58.32; H, 5.59; N, 6.48; S, 7.41. Found: C, 58.37; H, 5.79; N, 6.49; S, 7.62; Twice recrystallizaton of this ester with 74% ee from ethyl ether

provided **6′a** with 96% ee in 62% yield; mp 82–84°C; $[\alpha]_D^{20}=+127$ (*c* 1.1, $CHCl_3$), *S*; HPLC analysis using a Whelk-O1 column [*iso*-PrOH/hexane: 1:99; flow rate: 0.6 mL/min; detector: 254 nm] showed it to be 96% ee [t_R (*R*) 25.48 min and t_R (*S*) 27.44 min]. Using the same methodology, optical purity of *ent*-**6′a** was increased from 74% ee to 96% ee in 64% yield. $[\alpha]_D^{20}=-126.9$ (*c* 0.9, $CHCl_3$), *R*.

4.4.2. Compound 6′b. 96% Yield; light yellow solid; IR (KBr, cm^{-1}): 2960, 1734, 1541, 1343, 1270, 1163, 1073; ^1H NMR (200 MHz, $CDCl_3$) δ 0.94 (d, 6H, *J*=5.80 Hz), 1.61–1.89 (m, 3H), 2.15 (s, 3H), 3.22 (d, 2H, *J*=5.49 Hz), 5.48 (m, 1H), 6.95 (d, 2H, *J*=7.94 Hz), 7.27 (d, 2H, *J*=7.94 Hz), 8.94 (d, 2H, *J*=2.14 Hz), 9.21 (t, 1H, *J*=2.14 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.79, 23.64, 25.49, 30.36, 39.55, 43.07, 75.94, 122.78, 130.04, 130.46, 131.54, 132.44, 134.50, 137.52, 149.17, 162.70. Calcd for $C_{20}H_{22}N_2O_6S$: C, 57.40; H, 5.30; N, 6.69; S, 7.66. Found: C, 57.46; H, 5.25; N, 6.72; S, 7.54. A single recrystallizaton of this ester with 81% ee from ethyl acetate provided **6′b** with 98% ee in 80% yield; mp 81–82°C; $[\alpha]_D^{20}=+135.97$ (*c* 0.93, $CHCl_3$), *S*; HPLC analysis of **6a** obtained from hydrolysis of this ester (vide infra) using a Chiralcel OD-H column [*iso*-PrOH/hexane: 1:99; flow rate: 0.6 mL/min; detector: 254 nm] showed it to be 98% ee [t_R (*R*) 21.28 min and t_R (*S*) 22.58 min].

4.4.3. Compound 6′c. R_f 0.43 (EtOAc/hexane 1:4); light yellow solid; mp 90–91°C; 97% yield; IR (KBr, cm^{-1}): 2974, 1729, 1554, 1352, 1281, 1172, 1071; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3H, *J*=4.4 Hz), 1.17–1.30 (m, 16H), 1.81–1.93 (m, 2H), 2.39 (s, 3H), 3.22 (d, 2H, *J*=5.4 Hz), 5.66 (m, 1H), 7.32 (d, 2H, *J*=5.6 Hz), 7.53 (d, 2H, *J*=5.4 Hz), 9.15 (d, 2H, *J*=1.4 Hz), 9.24 (t, 1H, *J*=1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.55, 21.84, 23.07, 25.37, 29.58, 29.67, 29.75, 29.86, 29.91, 32.24, 34.60, 61.92, 71.97, 122.73, 124.19, 129.81, 130.40, 133.82, 140.43, 142.23, 148.75, 161.88. Calcd for $C_{26}H_{34}N_2O_6S$: C, 62.13; H, 6.82; N, 5.57; S, 6.38. Found: C, 62.21; H, 6.63; N, 5.55; S, 6.27. HPLC analysis using a Chiralcel OD-H column [*iso*-PrOH/hexane: 1:9; flow rate: 0.5 mL/min; detector: 254 nm] showed it to be 79% ee [t_R (*R*) 25.29 min, t_R (*S*) 28.62 min]. Attempts to improve optical purity of this ester by recrystallization from various solvents failed.

4.4.4. Preparation and recrystallization of 3,5-dinitrobenzoate of (2*S*)-1-[(*RS*)-*p*-toluenesulfinyl]-2-dodecanol 7′c. To a stirred solution of **6′c** with 79% ee (3 mmol) in dichloromethane (15 mL), kept at 0°C was added dropwise a solution of *m*-chloroperbenzoic acid (3.3 mmol) in dichloromethane (25 mL). The solution was stirred at 0°C, until the TLC showed no staring material, and washed with 2N NaOH (2×10 mL) and brine (2×10 mL). Organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated to give **7′c**; R_f 0.73 (EtOAc/hexane 1:1); light yellow solid; mp 98–102°C; 93% yield; IR (KBr, cm^{-1}): 2922, 1724, 1546, 1343, 1288, 1174, 1033; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3H, *J*=6.3 Hz), 1.18–1.47 (m, 16H), 1.76–1.99 (m, 2H), 2.23 (s, 1.41H), 2.39 (s, 1.59H), 3.10–3.35 (m, 2H), 5.65 (m, 1H), 7.23 (d, 0.94H, *J*=7.7 Hz), 7.33 (d, 1.06H, *J*=7.7 Hz), 7.50–7.56 (m, 2H), 8.98 (d, 0.94H, *J*=2.2 Hz), 9.17 (d, 1.06H, *J*=2.2 Hz), 9.22 (t, 0.47H, *J*=2.2 Hz), 9.26 (t, 0.53H, *J*=2.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.53, 21.88, 23.05, 25.13, 29.45, 29.64, 29.68, 29.82, 29.88, 32.22, 34.57, 59.31, 71.28, 122.61, 124.26, 129.63, 130.20, 133.50, 136.55, 145.20, 148.59, 161.60. Calcd for $C_{26}H_{34}N_2O_7S$: C, 60.21; H, 6.61; N, 5.40; S, 6.18. Found: C, 60.39; H, 6.51; N, 5.45; S, 6.08; HPLC analysis using a Whelk-O1 column [EtOH/hexane: 1:9; flow rate: 1.0 mL/min; detector: 254 nm] showed it to be 79% ee with the (S_c)-configuration [t_R (R_c, S_s or R_s) 19.65 min, t_R (S_c, S_s or R_s) 21.09 min, t_R (R_c, S_s or R_s) 26.15 min and t_R (S_c, S_s or R_s) 33.33 min]. **7′c** was recovered from a single recrystallization in dichloromethane–hexane in 53% yield; mp 108–109°C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3H, *J*=6.3 Hz), 1.18–1.42 (m, 16H), 1.75–2.00 (m, 2H), 2.23 (s, 0.45), 2.39 (s, 2.55H), 3.10–3.17 (m, 2H), 5.67 (m, 1H), 7.23 (d, 0.30H, *J*=7.7 Hz), 7.33 (d, 1.70H, *J*=7.7 Hz), 7.50–7.56 (m, 2H), 8.97 (d, 0.30H, *J*=2.2 Hz), 9.17 (d, 1.70H, *J*=2.2 Hz), 9.22 (t, 0.15H, *J*=2.2 Hz), 9.26 (t, 0.85H, *J*=2.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.55, 21.84, 23.07, 25.37, 29.58, 29.67, 29.75, 29.86, 32.25, 34.60, 61.92, 71.97, 122.73, 124.19, 129.81, 130.20, 133.40, 133.82, 142.23, 148.75, 161.89. HPLC analysis using the same conditions as described above was found to be >99% ee having the (S_c)-configuration.

4.5. General procedure for hydrolysis of 6′a,b and 7′c and sulfoxidation of 6

Hydrolysis. Compounds **6′a**,**b** and **7′c** (5 mmol) obtained after improvement of their optical purities by recrystallization was dissolved in methanol (50 mL), treated with 2N NaOH (50 mL) and stirred for 20 min at room temperature. After evaporation of methanol under reduced pressure, residue was extracted with ethyl ether (3×10 mL). The combined extract was dried over anhydrous $MgSO_4$, filtered and concentrated to give **6a**,**b** and **7c** in quantitative yields, respectively. The sulfanyl or sulfinyl alcohols obtained could be used for sulfoxidation or alkylation (vide infra) without further purification.

Sulfoxidation. To a solution of **6** (4 mmol) in dichloromethane (20 mL) was added dropwise a solution of *m*-chloroperbenzoic acid (4.4 mmol) in dichloromethane (30 mL) for 10 min at 0°C. After the mixture was stirred for 30 min at room temperature, organic layer was separated, washed with 2N NaOH (2×10 mL) and brine (2×10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated to give **7**, which could be used for alkylation without further purification.

4.5.1. (2*S*)-1-[(*RS*)-*p*-Toluenesulfinyl]-2-heptanol 7a. R_f 0.28 (EtOAc/hexane 1:1); oil; 92% yield; IR (neat, cm^{-1}): 3423, 2911, 1032; ^1H NMR (300 MHz, $CDCl_3$) δ 0.81–0.88 (m, 3H), 1.29–1.67 (m, 8H), 2.43 (s, 3H), 2.63 (dd, 0.45H, *J*=1.8, 13.4 Hz), 2.77 (dd, 0.55H, *J*=2.4, 13.1 Hz), 2.94 (dd, 0.55H, *J*=9.2, 13.1 Hz), 3.04 (dd, 0.45H, *J*=9.6, 13.6 Hz), 3.68 (d, 0.55H, *J*=2.75 Hz), 3.77 (s, 0.45H), 4.15 (m, 0.45H), 4.30 (m, 0.55H), 7.35 (d, 2H, *J*=7.94 Hz), 7.50–7.58 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.64, 22.15, 23.20, 25.34, 25.43, 32.21, 32.30, 37.65, 37.92, 61.63, 63.05, 67.54, 69.63, 124.69, 130.89, 142.27, 142.74. Calcd for $C_{14}H_{22}O_2S$: C, 66.10; H, 8.72; S, 12.61. Found: C, 60.13; H, 8.60; S, 12.43. In the same manner as above, (*R*)-**7a** was obtained from (*R*)-**6a** in 93% yield.

4.5.2. (2*S*)-4-Methyl-1-[(*RS*)-*p*-toluenesulfinyl]-2-pentanol 7b. R_f 0.31 (EtOAc/hexane 1:1); oil; 95% yield; IR (neat, cm^{-1}): 3394, 2955, 1018; ^1H NMR (300 MHz, $CDCl_3$) δ 0.79–0.96 (m, 6H), 1.13–1.86 (m, 3H), 2.43 (s, 3H), 2.63 (dd, 0.48H, J=1.8, 13.7 Hz), 2.75 (dd, 0.52H, J=2.4, 13.1 Hz), 2.93 (dd, 0.52H, J=9.0, 13.3 Hz), 3.02 (dd, 0.48H, J=9.5, 13.4 Hz), 3.02 (dd, 0.48H, J=9.5, 13.4 Hz), 3.58–3.74 (m, 1H), 4.25 (m, 0.52H), 4.41 (m, 0.48H), 7.35 (d, 2H, J=7.94 Hz), 7.54–7.57 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.14, 22.63, 22.71, 23.59, 23.86, 24.80, 24.97, 46.58, 47.00, 62.26, 63.43, 65.74, 67.81, 124.68, 130.78, 142.27, 142.73. Calcd for $C_{13}H_{20}O_2S$: C, 64.96; H, 8.39; S, 13.34. Found: C, 64.99; H, 8.39; S, 13.01.

4.5.3. (2*S*)-1-[(*RS*)-*p*-Toluenesulfinyl]-2-dodecanol 7c. R_f 0.35 (EtOAc/hexane 1:1); 42–43°C; 96% yield; IR (KBr, cm^{-1}): 3384, 2965, 1015; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3H, J=6.6 Hz), 1.22–1.59 (m, 18H), 2.44 (s, 3H), 2.64 (dd, 0.85H, J=1.9, 13.6 Hz), 2.77 (dd, 0.15H, J=1.8, 13.1 Hz), 2.94 (dd, 0.15H, J=9.6, 13.1 Hz), 3.06 (dd, 0.85H, J=9.6, 13.6 Hz), 3.79 (d, 0.85H, J=3.0 Hz), 3.89 (br s, 0.15H), 4.15 (m, 0.85H), 4.31 (m, 0.15H), 7.36 (d, 2H, J=7.8 Hz), 7.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.58, 21.85, 23.10, 25.55, 29.72, 29.78, 29.89, 29.97, 32.28, 37.37, 61.91, 66.80, 124.19, 130.27, 130.37, 139.49, 141.73. Calcd for $C_{19}H_{32}O_2S$: C, 70.32; H, 9.94; S, 9.88. Found: C, 70.41; H, 9.76; S, 9.69.

4.6. General procedure for alkylation

Under a nitrogen atmosphere, *n*-BuLi (5.6 mmol, 2.5 M in hexane) was added dropwise to **7a** or **7b** (2 mmol) in anhydrous THF (10 mL) at −78°C and the mixture was stirred for 30 min at the same temperature. To this, alkyl iodides (2.2 mmol) was added dropwise and the resulting mixture was stirred for 30 min at −78°C, allowed to warm to 20°C over 2 h, and then quenched by addition of saturated ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2×10 mL). The combined extract was dried over anhydrous Na_2SO_4, filtered and concentrated to give **8**–**10**. The crude alkylated products obtained were further purified by a flash column chromatography on silica gel (230–400 mesh).

4.6.1. (2*RS*,3*S*)-2-[(*RS*)-*p*-Toluenesulfinyl]-3-octanol 8. R_f 0.31 (EtOAc/hexane 1:1); oil; 93% yield; IR (neat, cm^{-1}): 3394, 2955, 1018; ^1H NMR (300 MHz, $CDCl_3$) δ 0.73–1.66 (m, 14H), 2.37 (s, 3H), 2.45 (m, 1H), 3.68 (m, 1H), 4.04 (m, 1H), 7.29 (d, 2H, J=7.94 Hz), 7.39–7.49 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 9.44, 14.61, 22.08, 23.15, 25.97, 32.15, 34.70, 62.52, 62.84, 70.06, 73.04, 125.54, 130.69, 139.35, 142.56. Calcd for $C_{15}H_{24}O_2S$: C, 67.12; H, 9.01; S, 11.95. Found: C, 67.29; H, 9.12; S, 12.02. Using the same methodology, *ent*-**8** was obtained in 90% yield.

4.6.2. (4*S*,5*RS*)-2-Methyl-[(*RS*)-*p*-toluenesulfinyl]-4-heptanol 9. R_f 0.41(EtOAc/hexane 1:1); oil; 76% yield; IR (neat, cm^{-1}): 3313, 2962, 1022; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84–2.01 (m, 11H), 2.42 (s, 3H), 2.72 (m, 1H), 3.60 (d, 0.28H, J=6.41 Hz), 4.13 (m, 0.28H), 4.28 (m, 0.72H), 4.53 (s, 0.72H), 7.33 (d, 2H, J=7.94 Hz), 7.46 (d, 0.56H, J=8.4 Hz), 7.61 (d, 1.44H, J=8.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.53, 12.94, 16.44, 20.00, 21.83, 24.21, 24.52, 24.57, 25.20, 44.17, 45.53, 70.14, 70.54, 71.92, 126.08, 130.75, 141.16, 142.82. Calcd for $C_{15}H_{24}O_2S$: C, 67.12; H, 9.01; S, 11.95. Found: C, 67.19; H, 9.19; S, 11.78.

4.6.3. (4*S*,5*RS*)-2-Methyl-[(*RS*)-*p*-toluenesulfinyl]-4-octanol 10. R_f 0.53 (EtOAc/hexane 1:1); oil; 72% yield; IR (neat, cm^{-1}): 3230, 2963, 1022; ^1H NMR (300 MHz, $CDCl_3$) δ 0.58–1.90 (m, 16H), 2.48 (s, 3H), 2.73 (m, 1H), 3.68 (m, 0.46H), 4.29 (m, 1H), 4.46 (m, 0.54H), 7.31–7.62 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.74, 20.66, 21.84, 22.91, 24.57, 25.18, 29.04, 30.37, 44.25, 67.62, 70.61, 71.05, 126.14, 130.74, 141.08, 142.81. Calcd for $C_{16}H_{26}O_2S$: C, 68.04; H, 9.28; S, 11.35. Found: C, 68.08; H, 9.25; S, 11.38.

4.7. General procedure for preparation of optically active pheromones 1–4 by desulfurization of 7′c and 8–10

According to the literature procedure,[19] a solution of each of **7′c** and **8**–**10** (2 mmol) in anhydrous methanol (10 mL) was added to a suspension of Raney-Ni (ca. 0.3 g) in anhydrous methanol. After the mixture was stirred for 6 h at room temperature, the Ni was removed by filtration on a celite short column. The filtrate was concentrated to give the product pheromones **1**–**4**, which were further purified by a flash chromatography on silica gel (230–400 mesh).

4.7.1. (*R*)-(−)-3-Octanol (*R*)-1. R_f 0.28 (EtOAc/hexane 1:4); oil; 89% yield; IR (neat, cm^{-1}): 3360, 2931; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, 3H, J=6.26 Hz), 1.06–1.41 (m, 14H), 3.80 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.66, 23.28, 24.11, 26.09, 32.50, 40.00; HRMS calcd for ($C_8H_{18}O^+-H_2O$): 112.1252. Found: 112.1258; $[\alpha]_D^{20}$=−11.51 (c 1.02, $CHCl_3$) *R*; {lit.[9] $[\alpha]_D^{20}$=−9.7 ($CHCl_3$), *R*, >99% ee}; GC analysis (column temperature: 40°C, isothermal; carrier gas: He; head pressure: 13 psi, flow rate: 1 mL/min; detector: FID) using a G-TA column (Astec) showed it to be 96% ee [t_R (*R*) 7.21 min and t_R (*S*) 7.64 min]. In the same manner as above, (*S*)-(+)-**1** with 96% ee was obtained; $[\alpha]_D^{20}$=+10.21 (c 1.02, $CHCl_3$) *S*; {lit.[9] $[\alpha]_D^{22}$=+10.1 ($CHCl_3$), *S*, >99% ee}.

4.7.2. (*R*)-(−)-2-Dodecanol (*R*)-2. R_f 0.37 (EtOAc/hexane 1:4); oil; 92% yield; IR (neat, cm^{-1}): 3381, 2959; ^1H NMR (200 MHz, $CDCl_3$) 0.88 (t, 3H, J=6.41 Hz), 1.18 (d, 3H, J=6.10 Hz), 1.27–1.41 (m, 19H), 3.79 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.75, 23.33, 24.11, 26.43, 29.99, 30.27, 32.56, 40.04, 68.87. Calcd for $C_{12}H_{26}O$: C, 77.35; H, 14.06. Found: C, 77.31; H, 14.08; $[\alpha]_D^{20}$=−6.53 (c 1.21, $CHCl_3$) *R*; {lit.[4] $[\alpha]_D^{20}$=−6.5 (c 1.11, $CHCl_3$), *R*, 100%ee}; GC analysis of its acetate (column temperature: 150°C, isothermal; He; head pressure: 13 psi, flow rate: 1 mL/min; detector: FID) using a β-DEX 120 chiral column (Supelco) showed it to be 99% ee [t_R (*R*) 39.09 min and t_R (*S*) 40.64 min].

4.7.3. (*R*)-(−)-2-Methyl-4-heptanol (*R*)-3. R_f 0.40 (EtOAc/hexane 1:4); oil; 89% yield; IR (neat, cm^{-1}): 3422, 2910; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (d, 3H, J=2.4 Hz), 0.93 (d, 3H, J=2.4 Hz), 1.16–1.53 (m, 10H), 1.74 (m, 1H), 3.67

(m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.75, 19.43, 22.71, 24.15, 25.27, 40.94, 47.50, 70.36; HRMS calcd for ($C_8H_{18}O^+-H_2O$): 112.1252. Found: 112.1230; $[\alpha]_D^{20}=-12.24$ (*c* 0.4, MeOH) *R*; {lit.[10] $[\alpha]_D^{22}=-11.9$ (*c* 1.04, MeOH), *R*, 99.1%ee; $[\alpha]_D^{22}=+13.3$ (*c* 1.11, MeOH), *S*, 97.6%ee}; HPLC analysis of its benzoate using a Chiralpak OT column [MeOH; flow rate: 0.3 mL/min; detector: 254 nm] showed it to be 98% ee [t_R (*R*) 25.94 min and t_R (*S*) 32.43 min].

4.7.4. (*R*)-(−)-2-Methyl-4-octanol (*R*)-4. R_f 0.45 (EtOAc/hexane 1:4); oil; 90% yield; IR (neat, cm^{-1}): 3360, 2900; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89–0.94 (m, 9H), 1.16–1.42 (m, 9H), 1.76 (m, 1H), 3.65 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.70, 22.68, 23.40, 24.13, 25.23, 28.45, 38.42, 47.45, 70.58; HRMS calcd for ($C_9H_{20}O^+-H_2O$): 126.1408. Found: 126.1389; $[\alpha]_D^{20}=-11.95$ (*c* 0.45, MeOH) *R*, >98% ee; {lit.[10] $[\alpha]_D^{22}=-10.5$ (*c* 1.17, MeOH), *R*, 99.1%ee; $[\alpha]_D^{22}=+11.6$ (*c* 1.04, MeOH), *S*, 97.6%ee}.

Acknowledgements

This study was supported by the Hallym Academy of Sciences at Hallym University (2002-21-03), Korea.

References

1. (a) Mori, K. *Chirality* **1998**, *10*, 578–586. (b) Mori, K. *Eur. J. Org. Chem.* **1998**, 1479–1486. (c) Mori, K. *Tetrahedron* **1989**, *45*, 3233–3298.
2. Cammaerts, M-C.; Mori, K. *Physiol. Entmol.* **1985**, *11*, 33–36.
3. (a) Brand, J. M. *J. Chem. Ecol.* **1985**, *11*, 177–180. (b) Cammaerts, M.-C.; Mori, K. *Physiol. Entmol.* **1987**, *12*, 381–385.
4. Mori, K. *Biosci. Biotech. Biochem.* **1992**, *56*, 1673. and references cited therein.
5. (a) Ramirez-Lucas, P.; Malosse, C.; Ducrot, P-H.; Lettere, M.; Zagatti, P. *Bioorg. Med. Chem.* **1996**, *4*, 323–330. (b) Perez, A. L.; Campos, Y.; Chinchilla, C. M.; Oehlschlager, A. C.; Gries, G.; Gries, R.; Giblin-Davis, R. M.; Castrillo, G.; Peña, J. E.; Duncan, R. E.; Gonzalez, L. M.; Pierce, Jr. H. D.; McDonald, R.; Andrade, R. *J. Chem. Ecol.* **1997**, *23*, 869–888.
6. Ohtani, T.; Nakatsukasa, H.; Kamezawa, M.; Tachibana, H.; Naoshima, Y. *J. Mol. Catal. B: Enzymatic* **1998**, *4*, 53–60.
7. Itoh, T.; Mitsukura, K.; Kanaphai, W.; Takagi, Y.; Kihara, H.; Tsukube, H. *J. Org. Chem.* **1997**, *62*, 9165–9172.
8. Baraldi, P. T.; Zarbin, P. H. G.; Vieira, P. C.; Corrêa, A. G. *Tetrahedron: Asymmetry* **2002**, *13*, 621–624.
9. Fujiwhara, M.; Mori, K. *Agric. Biol. Chem.* **1986**, *50*, 2925–2927.
10. Takenaka, M.; Takikawa, H.; Mori, K. *Liebigs Ann.* **1996**, 1963–1964.
11. For reviews, see: (a) Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; Wiley-VCH: New York, 1997. (b) Ramachandran, P. V.; Brown, H. C. In *Reductions in Organic Synthesis. ACS Symposium Series 641*; Abdel-Magid, A. F., Ed.; American Chemical Society: Washington, DC, 1996; pp 84–97. (c) Cho, B. T.; Chun, Y. S. In *Organoboranes for Syntheses. ACS Symposium Series 783*; Ramachandran, P. V., Brown, H. C., Eds.; American Chemical Society: Washington, DC, 2001; pp 122–135. (d) Itsuno, S. *Org. React.* **1998**, *52*, 395–576. (e) Itsuno, S. *Comprehensive Asymmetric Catalysts*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 3, pp 289–315. (f) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1986–2012. (g) Daverio, P.; Zanda, M. *Tetrahedron: Asymmetry* **2001**, *12*, 2225–2259.
12. NB-Enantride: (a) Midland, M. M.; Kazubski, A.; Woodling, R. E. *J. Org. Chem.* **1991**, *56*, 1068–1074. NB-Enantride=lithium B-*iso*-2-(2-benzyloxy)-ethylapopinocampheyl-9-borabicyo[3.3.1]nonyl hydride; Eapine-Hydride: (b) Ramachandran, P. V.; Brown, H. C.; Swaminathan, S. *Tereahedron: Asymmetry* **1990**, *1*, 433–436. Eapine-Hydride=lithium B-*iso*-2-ethylapopinocampheyl-9-borabicyclo[3.3.1]nonyl hydride; (2*R*,5*R*)-dimethylborolane/(2*R*,5*R*)-dimethyl-borolanyl methanesulfonate: (c) Imai, T.; Tamura, T.; Yamamuro, A.; Sato, T.; Wollmann, T. A.; Kennedy, R. M.; Masamune, S. *J. Am. Chem. Soc.* **1986**, *108*, 7402–7404. Enzyme: (d) Keinan, E.; Hafeli, E. K.; Steh, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 162–169.
13. (a) Ogura, K. In *Sulfa Stabilization. Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency in Modern Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon: Seoul, 1991; Vol. 1, pp 505–539. (b) Metzner, P.; Thuillier, A. *Sulfur Reagent in Organic Synthesis*; Academic: New York, 1994. (c) Walker, A. J. *Tetrahedron: Asymmetry* **1992**, *3*, 961–998.
14. Cho, B. T.; Choi, O. K.; Kim, D. J. *Tetrahedron: Asymmetry* **2002**, *13*, 697–703.
15. Sano, T.; Ohashi, K.; Oriyama, T. *Synthesis* **1999**, 1141–1144.
16. Diastereomeric ratios determined by ^{1}H NMR analysis of **7′c** before and after recrystallization found to be 53:47 and 85:15, respectively.
17. (a) Tanikaga, R.; Hosoya, K.; Kaji, A. *J. Chem. Soc. Perkin Trans. 1* **1988**, 2397–2402. (b) Takano, S.; Yanase, M.; Takahakshi, M.; Ogasawara, K. *Chem. Lett.* **1987**, 2017–2020.
18. Diastereomeric ratios determined by ^{1}H NMR analysis were 55:45 for **7a**, 58:42 for **7b** and 85:15 for **7c**.
19. Solladié, G.; Maestro, M. C.; Rubio, A.; Pedregal, C.; Carreño, M. C.; Ruano, J. L.; G, *J. Org. Chem.* **1991**, *56*, 2317–2322.